LARGE-SCALE CLINICAL TRIALS AND STUDY DEVELOPMENT

Teri Manolio, M.D., M.H.S.

I. Clinical trials: Rationale and preparatory work

   A. Object: to determine if an intervention (e.g., drug, operation, preventive measure, etc.) is associated with either:

      1. Change in the natural history of the disease under study;

      2. Improvement in response over other available therapy;

      3. Unacceptable side effects over other available therapy

   B. Design: to assign persons from a **well-defined** study population to treated or untreated groups **at random**, and then to observe them for a **specified time** for the occurrence of **well-defined endpoints**

   C. Scientific foundation for considering clinical trial

      1. Two (or more) treatment strategies available

      2. Neither of two (or more) treatment strategies known to be superior

      3. Good scientific evidence to support use of either strategy

         a. Ecologic studies

         b. Observational studies (concurrent or nonconcurrent)

         c. Animal data

         d. Small, tightly controlled therapeutic trials (phase I, phase II drug studies, metabolic ward studies)

II. Clinical trials: Randomization

   A. Definition: process for making a selection or assignment in which there is associated with every legitimate outcome in the selection or assignment process a known

probability

B. Reasons for random allocation

1. Eliminate selection bias

2. Assure any baseline differences in study groups arose by chance

3. Help to assure comparability not only on known confounders, which can be adjusted for, but (more importantly) on unknown confounders

4. Provide study groups with known statistical properties regarding baseline composition

5. Provide a statistical basis for certain tests of significance

C. Hallmarks of sound allocation schemes

1. Order of allocation is reproducible

2. Documented methods for generation and administration of schedule

3. Fail-safe feature to prevent release of assignment until essential conditions satisfied

4. Assignment remains masked to all concerned until it is needed

5. Future assignments cannot be predicted from past assignments

6. Departures from established procedures can be monitored

D. Alternatives to randomization

1. Non-random systematic schemes such as odd vs even numbered clinic days, every other patient, etc.

2. Pseudo-random schemes based on social security number, hospital number, or birthdate

E. Misconceptions regarding randomization

1. A haphazard procedure is the same as a random procedure

2. Randomization insures comparable study groups

3. Differences in the baseline composition of the study groups is evidence of a breakdown in the randomization process

4. It is possible to test for randomness

5. A study which does not involve random allocation is invalid

III. Subject Recruitment

A. "Facts of Life"

1. Early estimates of patient availability are usually unrealistically high

2. The likelihood of achieving a prestated recruitment goal is small and takes a major effort

3. Patients presumed eligible for study during planning can be expected to disappear mysteriously as soon as the trial starts

4. Recruitment will be more difficult, cost more, and take longer than planned

B. Necessary preparatory steps

1. Collect reliable data to estimate patient availability

2. If matching, allow for screening twice as many controls per discrete variable matched upon

3. Decide on general recruitment approach

4. Outline steps in recruitment process

5. Establish necessary contacts for recruitment

C. Recruitment mistakes and problems

1. Competing with private physicians for patients

2. Providing basic care rather than referring patient back to primary care physician

3. Failure to maintain adequate contact with referring physicians

4. Attempting recruitment without the support of colleagues

5. Taking access to medical records for granted

6. Failing to secure enthusiasm and commitment of staff

7. Inadequate publicity

IV. Introduction - How to carry out a study

A. Prerequisites

1. Study question defined

2. Design chosen

3. Sample size estimated

4. Availability of study subjects determined

B. To get going, must: write protocol
get human subjects approval
design data forms
pre-test forms, train interviewers
monitor data quality, treatment effects
provide for data entry and editing

V. Study protocol

A. Importance

1. Provides road map for performance of study

2. Forces investigator to anticipate problems

3. Facilitates communication with potential collaborators, employers, funding agencies

4. Assists in manuscript preparation

B. Components

1. Background and rationale

2. Specific objectives (3-5 aims of study)

3. Concise statement of design

4. Methods and analysis

5. Responsibility and authorship

C. Statement of design: Concise statement of what you plan to do
"An observational study of decline in pulmonary function in persons living in heavily industrialized areas compared to persons in non-industrial areas."

"A prospective, nonconcurrent study of postoperative pneumonia in patients receiving regional vs. general anesthesia for peripheral vascular grafting."

D. Methods

1. Definition of patient population: as specific as possible (but not too restrictive), specify both cases and controls

a. Inclusion criteria

1. Participants must have <u>at least one</u> of specified criteria

2. Usually include disease or condition under study (prior myocardial infarction, smokers, etc.), age, sex, area of residence or hospitalization, etc.

b. Exclusion criteria

1. Participants must not have <u>any</u> specified criterion

2. Generally include conditions making study difficult or impossible

a. Patients in whom one treatment or other is inappropriate or unethical (e.g., Coronary Artery Surgery Study excluded patients with left main coronary artery disease)

b. "Logistic" concerns (e.g., aged under 18, critically ill, emergency hospitalization)

c. Circumstances making determination of outcome difficult or impossible (e.g., left bundle branch block in study of ECG-ischemia, expected to leave area or die within short time, unable to communicate)

c. Common mistakes concerning the study population

1. Unnecessary exclusion criteria and needlessly restrictive inclusion criteria

2. Plans for the trial made without any reliable data on patient availability

3. Unrealistic timetable for recruitment or no recruitment goal

4. Revision of sample size calculations to make them consistent with recruitment realities

2. Outcome definition: as specific and clear as possible

a. Primary vs. secondary outcomes

b. Standard clinical definitions

1. Textbook: usually not specific enough

2. Consensus conference (definition of hypertension)

3. Recognized expert body (WHO, AHA)

4. Appointed panel of experts

5. Previous widely-recognized study (HDFP, LRC, CASS)

c. If unforeseen occurs, submit to panel of masked, unbiased "experts"

D. Treatment definition

1. Specify as much as possible without interfering with patient management

2. Realize that generalizability often lost in quest for specificity

3. Specify criteria for withdrawal from study or deviation from protocol

4. List concurrent medications, procedures, etc. that are prohibited or permitted

5. Masking

a. Specify whom to be masked, why, how, and to what

b. Assess effectiveness of masking

c. Specify criteria for unmasking, whom to be unmasked

d. Most appropriate in observational studies to mask determination of outcome so that reviewers are unaware of unnecessary aspects-- provide information on "need to know" basis

E. Methodology: as specific as possible, should permit another investigator to step into study (or reproduce it) at any time

1. Which data to be collected, how

2. Timetable for follow-up

3. Specifics of laboratory methods

a. Enzyme determinations: what laboratory methods, etc.

b. Chest x-rays: PA and/or lateral, supine or erect, etc.

c. Clinical measurements: BP supine or standing, heart sounds in left lateral decubitus, etc.

F. Informed consent (see below, also separate lecture)

G. Data to be collected (separate lecture)

H. Data analysis: primary outcome, associations to be studied, univariate or multivariate techniques to be used, computer package, data entry

J. Policy on oral or written presentation of results, responsibilities of investigators

K. Revisions as needed, dated, with replacement pages

L. Special problems during course of study

1. Changes in inclusion or exclusion criteria

2. Changes in data collection procedures

3. Drift in measurements

4. Change in health and treatment patterns or practices within the community

VI. Protection of subjects and informed consent

A. Protection of subjects

1. Monitoring for adverse effects

2. Informing patient, physician of complications or abnormalities
3. Interim analyses

B. Consent procedures

1. Written informed consent

2. Institutional review board (IRB): independent review and monitoring by panel including members outside institution

3. Approach

a. Find proper setting: quiet, private

b. Provide adequate time

c. Encourage patient to discuss with others (family members, physician), ask questions

d. Ensure patient's competence to give consent

e. Provide copy of signed consent

5. Common mistakes in the consent process

a. Inadequate time

b. Failure to specify required procedures

c. Inadequate documentation

d. Vague or inaccurate statements

e. Making commitments which cannot be met

f. Use of untruths to protect study design

g. Consent after the fact

h. Speaking for the patient ("I understand that...")

VII. Data Management - Subject Record

A. Each participant should have his or her own study record stored in locked area when not in use

B. Each participant should have a study number for use as identifier-- name should not be on computer tape, coding forms, etc.

C. If multiple data sources are needed, use separate forms and system to keep track of progress in data collection (e.g., colored dots, transmittal forms, etc.)

VIII. Subgroup analysis

A. Purposes

1. Often performed when no overall effect found

2. Used to look for high-risk or peculiar groups with marked treatment effect

3. Beware of "data-dredging"-- looking at many, many subgroups until one "significant" effect found

B. Standards

1. Limit choice of subgrouping variables to baseline characteristics

2. Look at all members of the subgroup

3. Distinguish between a priori and a posteriori selected subgrouping variables

4. Choose cutpoints which are independent of treatment differences (if blood pressure treated to goal of 140/90, cutting blood pressure at 140 vs. > 140 will introduce bias of successful vs. unsuccessful treatment)

5. Use stringent significance testing, especially if number of hypotheses tested is large

6. When possible, validate findings before reporting on an a posteriori (data-driven) subgrouping variable

7. Report methods and procedures

8. Be cautious regarding conclusions

Appendix - Components of Good Clinical Trials Report
(after Dr. Curtis L. Meinert, Professor of Epidemiology,
Johns Hopkins School of Hygiene and Public Health)

I. Design should specify:

A. Purpose of study
B. Primary outcome measure
C. Test and control treatments
D. Level of treatment masking: unmasked, single- or double-
E. Planned recruitment goal
F. Eligibility and exclusion criteria
G. Method of patient recruitment
H. Number of patients enrolled
I. Number of patients in analyses (should equal the number allocated to treatment, or explanation should be given)
J. Method of treatment allocation
K. Stratification variables
L. Methods of measuring treatment adherence
M. Planned and actual length of patient follow-up

II. Patient safeguards should include:

A. Informed consent, Institutional Review Board (IRB) approval
B. Measures taken to protect patient confidentiality
C. Procedures to monitor study results for evidence of treatment effects

III. Data collection schedule

A. Frequency of baseline visits
B. Frequency of follow-up visits
C. Definition of dropouts

IV. Results should include:

A. Number of patients enrolled by treatment group
B. Number of deaths observed
C. Comparison of treatment groups for the primary outcome measure
D. Indicators of the completeness of follow-up by treatment group
    1. Number of missed examinations
    2. Number of dropouts and withdrawals
    3. Number of patients lost to follow-up
E. Assessment of the comparability of the treatment groups with regard to selected

baseline characteristics

F. Multiple regression analyses using baseline characteristics to provide adjusted treatment comparisons

G. Treatment comparisons by level of adherence

V. Conclusions should specify:

A. Test of primary hypothesis/outcome
B. Test of secondary hypotheses as applicable
C. Limits on generalization of the results indicated
D. Discussion of statistical power if no treatment difference is detected

CLINICAL TRIALS AND STUDY DEVELOPMENT

Teri Manolio, M.D., M.H.S.

Lecture Assessment

1. Which of the following should be included in a study protocol?

   a. Specific objectives (3-5 aims of study)

   b. Description of methods and proposed analyses

   c. Sample size estimate

   d. All of the above

2. Which of the following is <u>most</u> important in developing exclusion criteria for a clinical trial?

   a. Conditions (i.e., disease, patient characteristics) making one of the proposed treatments inappropriate or unethical

   b. "Logistic" concerns (e.g., aged under 18, critically ill, emergency hospitalization)

   c. Conditions making determination of outcome difficult or impossible

   d. Conditions likely to reduce sharply the availability of subjects for the study

3. Which of the following are critical mistakes to be avoided in planning clinical trials?

   a. Unnecessary exclusion criteria and needlessly restrictive inclusion criteria

b. Plans for the trial made without any reliable data on patient availability

c. Unrealistic timetable for recruitment or no recruitment goal

d. All of the above

4. Which of the following is not a necessary condition for selecting an appropriate control treatment?

   a. Application of the particular control treatment proposed must be ethical

   b. Availability of evidence indicating that the control treatment chosen to represent standard medical practice is indeed "standard"

   c. Ability to mask the administration of chosen control treatment
   d. Ability of any patient in the trial to receive the control treatment if so allocated

5. Suppose you were interested in determining the effect of aspirin on risk of stroke after myocardial infarction, and decided to test it in a randomized clinical trial of aspirin in post-MI patients.
   a. State the primary hypothesis of the trial.
   b. Specify two inclusion criteria for patients eligible for the trial.
   c. Specify four exclusion criteria for patients ineligible for the trial.

6. Why is random allocation to treatment desirable in clinical trials?

   a. To eliminate baseline differences in treatment groups

   b. To assure any baseline differences in treatment groups arose by chance

   c. To eliminate bias in classification of outcomes

   d. To eliminate bias in measurement of baseline characteristics

7. (from Hennekens and Buring, Epidemiology in Medicine, Little, Brown and Co., Boston,

1987)

In the Physicians' Health Study [Hennekens CH and Eberline K, Prev Med 1985; 14:165-8], 22,071 male physicians were randomized and mortality was postulated to be 70% that of white males in the general population. During the first 2 years, mortality was less than 25% rather than the anticipated 70%.

a. How do you explain these findings?

b. What could be done at that stage of the trial to increase the power of the study to maximize the chances of observing the small to moderate effects of aspirin use that were anticipated?